

REMARKS

Status of Claims

Claims 18-35 are all the claims pending in the application.

Withdrawn Rejections

Applicants thank the Examiner for withdrawing the provisional nonstatutory obviousness-type double patenting rejection.

Response to Rejections Under 35 U.S.C. § 103

Claims 18 and 20-25 remain rejected under 35 U.S.C. § 103 as being unpatentable over Ralph et al. and Lukas et al., for the reasons set forth in the Office Action mailed August 18, 2008.

In addition, claims 19 and 26-35 remain rejected under 35 U.S.C. § 103 as being unpatentable over Ralph et al. and Lukas et al., and further in view of Wadhwa et al. for the reasons set forth in the Office Action mailed August 18, 2008.

Applicants' arguments and the Declaration of Dr. Mackay, that one of skill in the art would have understood that Ralph was based on the release of cancer cells, their debris, or cellular components into the blood system to result in direct interaction between cancer cells and the blood cells to affect gene expression, was found to be not persuasive for the following reasons.

(1) The Office Action asserts that Applicants' arguments and the Declaration by Dr. Mackay are in direct contrast to the explicit teachings of Ralph at column 5, lines 7-11 that since markers are produced by circulating leukocytes and not diseased cells, detection may be feasible at very early stages of disease progression when there are few or no circulating cells present in the peripheral blood.

(2) The Office Action asserts that the passages from Ralph relied upon by Dr. Mackay to assert that direct contact between the sample to be analyzed and the diseased cells is necessary in Ralph relates to immunodetection assays, and not the identification of markers based upon mRNA expression. The Office Action asserts that Ralph discusses the identification of markers based on differential mRNA expression, and that there is no requirement that there be direct interaction between cancer cells, their debris, or cellular components.

(3) The Office Action asserts that Dr. Mackay's Declaration is contraindicated by the express teachings of Ralph and the general knowledge that one of ordinary skill in the art would have known that white blood cells spend most of their time outside the circulatory system, patrolling interstitial fluid and the lymphatic system as evidenced by Campbell (Biology, 4th Edition, 1996, page 833).

In response, and as previously argued, "[e]vidence showing there is no reasonable expectation of success may support a conclusion of nonobviousness." M.P.E.P. 2143.02. In this respect, the teachings of Ralph require direct contact between blood and cancer cells to elicit detectable changes.¹ One of ordinary skill in the art would not have expected to successfully diagnose very early stage breast cancer as with the claimed method which is based upon obtaining a display of altered gene expression from blood where no direct contact between the blood cells and disease cells is involved.

¹ As previously asserted, the method of Ralph is concerned with a comparison of gene expression levels in blood samples from patients with metastatic cancer which involves direct contact of blood cells with metastatic diseased cells in order to elicit an immune response that is detectable in the peripheral blood mononuclear cells (PBMCs). Further, there is no teaching or suggestion by Ralph to obtain probes from breast cancer patients using blood not in direct contact with cancer cells, or to prepare a gene transcript pattern for the diagnosis of cancers using such probes, as presently claimed. In fact, Ralph teaches generating probes from blood samples of patients with metastatic cancer.

Ralph as a whole does not teach or suggest detection of non-metastatic or pre-metastatic very early stage breast cancer

With regard to (1), as discussed in the previous Declaration and the present Supplemental Declaration by Dr. Mackay (submitted herewith), debris or cellular components present in peripheral blood (in which no diseased cells may be present) may provide the necessary trigger for the effect observed in Ralph. This debris is not, however, seen in very early stage breast cancer (see paragraph 6 in the Supplemental Declaration).

The Office Action has failed to consider the teachings of Ralph² as a whole. M.P.E.P. § 2141.02. Instead, the Office Action appears to separate, and interpret the disclosure in Ralph that detection may be feasible at very early stages of disease progression when there are few or not circulating cells present in the peripheral blood, on its own. As discussed in the Supplemental Declaration (see paragraphs 7-14 of the Supplemental Declaration), one of ordinary skill in the art would have appreciated and taken this disclosure in context with the rest of the teachings in Ralph, which is principally concerned with analysis of cancers that have reached metastatic potential or are metastatic. In this regard, these cells would reflect an altered phenotype and would have begun to release cells, debris or cellular components into the blood system allowing for the interaction of blood cells with the cells, debris or cellular components.

Accordingly, one of ordinary skill in the art would only have extrapolated these teachings to other cancers that are at a similar stage, i.e., cancers which have reached a metastatic phenotype and hence have detectable markers of that metastatic phenotype. As discussed in

² As previously acknowledged by the Office Action, Ralph does not teach or suggest a method in which (1) the cancer is very early stage breast cancer (see page 6, 3rd full paragraph of Office Action mailed February 8, 2008), (2) at least 10 differently expressed markers are isolated, and (3) 50 and 100 or between 10 and 50 markers are selected (see page 4, lines 12-15 of Office Action mailed August 18, 2008).

paragraph 12 of the Supplemental Declaration, Ralph uses this terminology in relation to a metastasizing tumor. Thus, it is clear that based upon the teachings of Ralph, one of ordinary skill in the art would not have extrapolated the method of Ralph for the detection of cancers which had not reached a metastatic phenotype, e.g., very early stage breast cancer, as claimed. Such an extrapolation would constitute impermissible hindsight. M.P.E.P. § 2145.

One of ordinary skill in the art would not have had a reasonable expectation of success of detecting very early stage breast cancer based upon the disclosure of Ralph

Additionally, as discussed in paragraph 15 of the Supplemental Declaration, one of ordinary skill in the art would not be motivated to try the method disclosed by Ralph to detect cancers that have not yet reached their metastatic potential, because there would have been no reasonable expectation of success of obtaining the claimed invention. It was known in the art that very early stage breast cancer, for example, has not reached this stage and can not be expected to be detectable by a method reliant on detection of metastatic markers which would be absent in such non-metastatic or pre-metastatic cancers. As discussed in paragraph 16 of the Supplemental Declaration, the present invention allows for the detection of cancers by detection of the pre-metastatic or non-metastatic state of the tumor. In contrast, Ralph may only be extrapolated to identifying early metastatic changes. The present invention is not foreshadowed by Ralph and offers a considerable contribution to the art in which early detection is vitally important to improving survival statistics. Thus, it would not have been obvious to extend the teachings of Ralph to all organ defined cancers such as very early stage breast cancer even in light of Lukas³ and Wadhwa⁴.

³ Although Lukas teaches markers or differentially expressed genes for very early stage breast cancer, Lukas is a deficient reference because Lukas is silent as to whether blood cells in a patient ... (footnote continued)

With regard to (2), in which Dr. Mackay's reference in the previous Declaration concerning the disclosure at column 47, lines 17 to 26 and column 52, lines 1 to 4 of Ralph is asserted to be directed to a section discussing immune detection assays rather than the identification of gene markers, Applicants note that as discussed at paragraph 18 of the Supplemental Declaration, modification of transcript levels acts as a trigger for alteration of antigen levels. Furthermore, the passage at column 52 of Ralph is clearly not concerned with antigen detection since this refers to the effect on gene expression. Thus, this disclosure in Ralph concerning direct contact cannot be dismissed or separated from the rest of the disclosure of Ralph since this teaching is the stated basis of both the transcript variation as well as any variations in the proteins that are expressed.

With regard to (3), in which Campbell is relied upon for the contention that one of ordinary skill in the art would have known that white blood cells would come into contact with tumor cells via the interstitial fluid and the lymphatic system even if no blood vessels invaded the tumor, Applicants assert that mere contact between a blood cell and a tumor cell is not enough to allow detection by Ralph. As discussed at paragraphs 19-21 of the Supplemental Declaration, pivotal to the success of the method by Ralph is the requirement for the cancer cell to have reached metastatic potential and thus, to display a metastatic phenotype. It is this metastatic phenotype which is detected or detectable by Ralph. Thus, even if blood cells did

with breast ductal carcinoma would have modified expression, or that such modified expression has diagnostic value. At most, Lukas teaches that tumor cells exhibit altered expression.

⁴ Because Wadhwa is merely relied upon by the Office Action for teaching a technical assay, i.e., reverse Northern assay of DNA fragments isolated from differential display, the addition of Wadhwa does not render the claimed invention obvious to one of ordinary skill in the art.

come into contact with very early stage breast cancer cells, no response of the kind observed by Ralph would have been expected, as those cells would not have reached metastatic potential.

Accordingly, because Ralph is concerned with demonstrating a diagnostic ability for cancers which are starting to be, or have already become metastatic, one of ordinary skill in the art would not have had a reasonable expectation of success of detecting very early stage breast cancer as claimed by modifying the teachings of Ralph with Lukas. As discussed in paragraph 22 of the Supplemental Declaration, there is nothing in Ralph that would have guided one of ordinary skill in the art to make the leap to the detection of cancers which are phenotypically different and which have not reached metastatic potential. The present invention allows for the *unexpected and surprising* detection of cancers which would not have been thought possible to detect based upon the method of Ralph.

Thus, the Office Action has failed to establish a *prima facie* case of obviousness. Neither Ralph, Lukas, nor Wadhwa, separately or in combination, teaches or suggests all the presently claimed limitations.” M.P.E.P. § 2143. Further, because neither Ralph, Lukas, nor Wadhwa teaches or suggests that very early stage breast cancer may be detected or diagnosed using non-metastatic or pre-metastatic cancer cells, one of ordinary skill in the art would not have been motivated, or had a reasonable expectation that the combination would successfully diagnose very early stage breast cancer.

Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

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